American Journal of Pharmacy

AND THE SCIENCES
SUPPORTING PUBLIC HEALTH

DR. E. FULLERTON COOK
United States Representative on the Expert Committee
on the Unification of Pharmacopoeias

Since 1825 May 1950

American Journal of Pharmacy

Published monthly by the Philadelphia College of Pharmacy and Science
43d Street, Kingsessing and Woodland Avenues, Philadelphia 4, Pa.

Annual Subscription, $4.00 | Foreign Postage, 25 Cents Extra
Single Numbers, 40 Cents | Back Numbers, 50 Cents

Entered as Second-Class Matter March 27, 1937, at the Post Office at Philadelphia, Pa.
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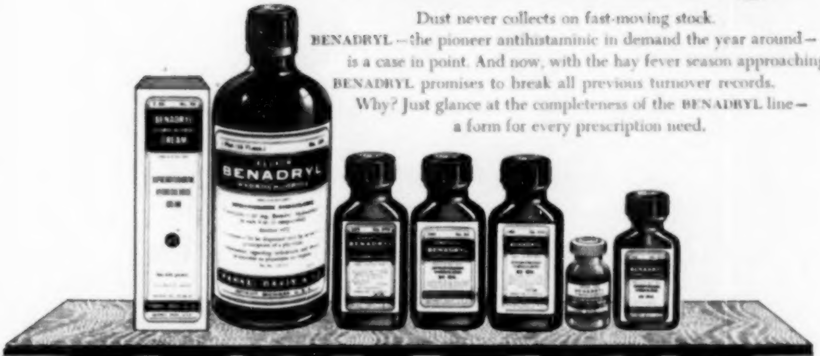

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AMERICAN JOURNAL OF PHARMACY

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Vol. 122 MAY 1950 No. 5

CONTENTS

Editorial

The International Pharmacopoeia 168

Articles

The Manufacturing of Parenteral Solutions. By L. Gershenfeld 171

Possibilities of Improving Nicaraguan Ipecac Root by Selection. By E. C. Higbee and J. W. Kelly 184

Selected Abstracts 189

Book Reviews 200

EDITORIAL

THE INTERNATIONAL PHARMACOPOEIA

AFTER many years of effort the first International Pharmacopoeia is about to become a reality. The completion of the English version has been announced by the WHO's Expert Committee on the Unification of Pharmacopoeias. The issuance of this version is to be delayed until the completion of the French text so that both may be published simultaneously.

The movement for a unified system of nomenclature and greater uniformity in drug standards dates back to 1902 when an International Conference for the Unification of Potent Remedies was held. In Brussels in 1906 and later in 1925 agreements were reached establishing certain standards for strength and nomenclature and these "International Protocol" standards have been used as a guide in the preparation of a number of national pharmacopoeias.

The old League of Nations established a commission to prepare an international pharmacopoeia but this work was interrupted during the last war. With the establishment of the World Health Organization as a part of the United Nations' program, the project of preparing an international pharmacopoeia became one of its assigned functions. An Expert Committee on the Unification of Pharmacopoeias was set up with Dr. C. H. Hampshire of the British Pharmacopoeia Commission as its chairman. The first International Pharmacopoeia is tangible evidence of this committee's work. Further work leading to the preparation of supplements has been undertaken in order to expand the scope and usefulness of the International Pharmacopoeia.

Although the book itself has not appeared, there already has been a number of frightened cries and strongly worded resolutions by those who fear the loss of autonomy of national pharmacopoeias now that an international text is being released. The basis for these fears is the same as that which underlies much of the opposition to international agreements in the political and economic fields. Human beings the world over have had nationalism and love of one's own country drilled into them by the politicians for so long that anything having the slightest tinge of international organization is distrusted

and feared almost instinctively. The majority of politicians are flag-waving nationalists since it is a risky business to try to convince the people back home that international agreement is the last remaining hope for civilization. It is much more simple to inflame their prejudices and picture oneself as a 100 per cent American, or whatnot, who will gladly die for his country, be it right or wrong.

Possibly it is too much to expect our politicians to be world statesmen. Their background and training is rarely such that we could expect them to have breadth of vision. Then, too, world statesmen in our national political system could hardly survive an election with dyed-in-the-wool and skillful politicos as their opponents. The fact is, however, that the world is in critical need of statesmen, in every country, men who see in chauvinism the terrible menace that it is and are willing to take a stand against it. Too many of our own members of Congress think that anything that hurts their constituents even slightly, *ipso facto,* is a bad thing for the country. Thus, if the importation of some "cheap" foreign product hurts domestic producers, a protective tariff must be applied. No thought is given to the economic and political impact of such a tariff barrier on the other country where it may well be the cause of a major catastrophe, cause a friendly government to fall and bring about a new government pledged to hate all things originating in the United States. The time has come when we must be willing to make reasonable sacrifices of our national economy and prerogatives in the interests of world peace and understanding, a third and perhaps final world war is the only alternative.

Those of us who have an interest in Pharmacopeial affairs need not plan the abandonment of the United States Pharmacopeia now that the International Pharmacopoeia has been developed. We should, however, set an example of friendly cooperation and do everything possible to raise the prestige and standing of the International Pharmacopoeia in the eyes of the world. By so doing the International Pharmacopoeia, which is but a minor activity of the United Nations, might well set a shining example of how nations can work together with mutual trust and understanding.

L. F. TICE

World Health Organization Committee on Unification of Pharmacopoeias

Left to right, are: (seated) Dr. I. R. Fahmy, Professor at Fouad University, Cairo, Egypt; Professor E. Fullerton Cook, Chairman of the Commission of the Revision of the Pharmacopoeia of the United States; Dr. C. H. Hampshire, Chairman and Secretary, from London; Dr. H. Baggesgaard-Rasmussen, from Denmark; (standing) Dr. G. A. Morrell, of Department of Health, Canada; Dr. Mayoral Pardo, of the University of Mexico; Dr. D. Van Os, of the University of Groningen, Netherlands; Dr. H. Flueck, of Switzerland, Dr. R. Hazard, of the University of Paris, France; and Mr. P. Blanc, Secretary and Chief of the Pharmaceutical Section of WHO.

UNations Photograph

THE MANUFACTURING OF PARENTERAL SOLUTIONS

By Louis Gershenfeld *

THE injection or introduction of solutions or suspensions of drugs or chemicals beneath the skin or mucous membranes is spoken of as parenteral administration.

Among the many reasons for the employment of the parenteral route are: (1) the need of prompt or quick action, (2) in patients who cannot or will not swallow or where absorption of the medication cannot be achieved due to disease or injury of the gastrointestinal tract, (3) where oral medication is useless or less effective since potency of the therapeutic agent is reduced or destroyed, (4) when a definite or exact blood level content is to be assured, and (5) for certain medicaments possessing a short duration of action and a low margin of safety.

There are many hazards in the use of parenteral therapy which are not encountered when other routes of administration are employed. The manufacturer's most important responsibility is the assurance that the parenteral solution is not contaminated by microorganisms, which eliminates it as a source of infection. Injectable solutions or suspensions represent a modern form of medication and are available either as ampuls, one-dose bulk solutions, cartridges and as multiple-dose vials.

Manufacturing Conditions

It is essential that parenteral solutions be prepared with the utmost care and strict attention to all details. They require the highest degree of technical control, and these controls should be frequently subjected to the closest scrutiny. The producer must surround his operations with proper safeguards in keeping with the latest accepted scientific and technical knowledge to be assured at all times that his parenteral solutions are the best which good manufacturing practice can produce.

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* Director, Department of Bacteriology, Philadelphia College of Pharmacy and Science. Member, Sterile Products Advisory Board United States Pharmacopoeia.

It is most important that the personnel in the parenteral department be competent or specially trained in all aspects of their specific duties. Everyone, including janitors, must be made and kept conscious of the need for cleanliness, asepsis, sterility and personal hygiene. It is a good practice to have them thinking constantly that they are part of a team preparing an injectable solution for one of their dear ones who is desperately ill. In most instances those who receive medication parenterally are sick, and they expect to be injected with solutions prepared with the utmost care. The supervisor must be an individual who possesses the necessary background, ability and personal characteristics which equip him to give continuous attention to, and efficient appraisal of, all plant operations and control procedures.

Parenteral Department

If the parenteral department is one of several divisions of a pharmaceutical manufacturing plant, it is good practice to have this department housed in a small building as a unit by itself. Where this is not practical, the rooms or unit should be segregated from quarters where other types of manufacturing operations are in progress. One should think of this unit as requiring even more attention than the Central Sterile Supply Department in large hospitals or isolation rooms either in large or small hospitals.

All areas should be kept immaculately clean at all times. From a sanitary viewpoint, the quarters must be kept above criticism. The watchword must be strict cleanliness.

Rooms (Compounding and Filling)

The most important areas in this department are the rooms where the solutions are prepared and the filling rooms. The latter may be cubicles or booths where solutions are not sterilized in the final container but sterilized in bulk by bacteriological filtration (with bacteria-excluding filters) and the filling and sealing operations are carried out aseptically.

Strict attention must be given to the construction of the room or cubicle. The filling rooms or cubicles should be small, compact, dust-free and closed. Here and elsewhere, the rooms should be designed to eliminate or at least minimize the possibility of dirt and dust collection and to permit easy cleaning. Sloped ceilings and rubber tile or special composition floors are desirable.

In the filling rooms, the amount of permanent equipment and furniture should be kept at a minimum. The conventional work bench is not satisfactory. Movable metal chairs are recommended, and table legs should be avoided. Wherever possible the table top should be stainless steel.

The rooms should be air-conditioned and under a slight positive pressure. They should be equipped with effective sterilamps or so-called germicidal lamps properly placed. To be assured of the maximum efficiency of ultraviolet light, the lamps should be kept burning continuously or at least during the working day and turned on each time at least 2 hours before the rooms are to be used. All lamps should be tested at 3 or 4 month intervals to be assured of their effectivness. Manufacturers of these lamps frequently cooperate through their service department in periodic checks. Janitors, who are specially trained, should be instructed to carefully wipe all lamps to remove layers of dust and other material. Janitorial work should be done at night or at the end of the working day. Rooms are wiped or swabbed with a solution of a suitable disinfectant every morning, one-half to one hour before the operations therein are started.

Everyone in the filling rooms should wear sterile gowns or uniforms and suitable sterile head covering (hood and mask), all made from lint-free material. Gowns with tight-fitting sleeves, stockinette type, are preferred. Each worker should wear a separate pair of clean shoes used only for this purpose which, when not in use, are kept in a suitable cabinet under ultraviolet light irradiation. Operators having upper respiratory infections, skin affections, or who are carriers of pathogens should be excluded from the filling rooms. A supervisor or other worker entering the latter when in operation, should also wear sterile gown and sterile head covering. It is advisable to have a signal system (buzzer, light or other device) for use when supplies are to be brought into the room.

A routine system of exposing Petri dishes containing blood agar (and also other suitable media for spot checking) at known, designated positions in the filling rooms should be practiced. The plates are exposed at least once or twice weekly for 15 to 30 minutes (or all operations during aseptic filling even for the entire period of operation) and then incubated. Statistical data should be compiled on the basis of one (or preferably more) month records of at least six daily plate exposures. An average count per plate (not over 5)

and an average total count of all plates per operation (less than 20 for sterile fill and not over 25 for other operations) are noted. Such a testing system is invaluable as an aid in determining the effectiveness of techniques, equipment, etc.

The effectiveness of an aseptic fill set-up can be strikingly revealed to the operators if the operation in all its details is conducted with a fluid culture medium (meat-infusion broth or thioglycollate medium being used as the parenteral preparation). The sealed ampuls or containers are then incubated to detect the presence or absence of growth of microorganisms.

Compounding

(a) The quarters or room where solutions are prepared should be adequate. Here as elsewhere and throughout the entire unit, any layout that may result from incomplete planning will lack essentials which later will be missed. If possible stainless steel equipment should be used throughout or at least as a top covering for all tables, counters, sinks, etc. All apparatus and equipment should be kept clean and thorough cleanliness is to be the watchword at all times. This room should not be a stock room for empty containers, bulk chemicals on other bulk materials and apparatus used infrequently. Only the real essentials should be kept here. Clean, lint-free gowns, laboratory coats or uniforms should be worn. At no time should shipments be unpacked in this room. This will minimize the amount of dirt, dust, fibers, etc. Fibers from the clothing of people, packings, boxes, wood floors and on paper may find their way in to the room and float in the air. These may get into finished solutions. Fibers and other foreign material may actually come from the air supplied to the room. Air filtration and the use of special air-filters or of closed systems may be necessary.

(b) Hands should never be placed on chemicals or raw materials, and spatulas or scoops must be clean before use. Chemicals or drugs should be of the highest grade available. This quality is frequently better than U. S. P. or N. F. or that used for oral preparations. If dirt, dust, debris or any foreign matter is present, chemicals should be purified if possible or rejected and not used. Portions of chemicals dropping on the table, balance pans, etc., are discarded. For assurance that the raw materials are of the best quality, one cannot rely solely upon high regard of the source of supply and upon written guarantees from the latter. Well planned and careful analyses

of each batch of raw materials should be carried out, even if only spot-checks are performed upon some of them.

(c) Water used for compounding should be at all times pyrogen-free distilled water (Injection Water or Water for Injection). On a small scale, distilled water can be obtained the same day directly from the still. If not used immediately, the water should be collected in chemically clean pyrex containers and properly covered or stoppered to avoid contamination with fibers, dust, etc. If, on a small scale, injection water for compounding cannot be used the same day, it should be autoclaved or otherwise sterilized. Large quantities of injection water required for compounding can be obtained by keeping pyrogen-free freshly distilled water as hot as possible in glass-lined tanks until used. Pyrogen-free water which was allowed to stand around in tanks at room temperature without prior sterilization should not be used. The quality of freshly distilled water depends not only upon the type of still used, but also upon the intelligence and reliability of the personnel in charge of its operation. The supervisor should familiarize himself with all concepts of the process of distillation and with the proper operation, frequency of cleansing and careful maintenance of the specific type of still used. In turn he should impart this information in all its details to those entrusted with its care, so that everyone will be familiar with the proper operation of the still.

There are only a handful of parenteral solutions in which it is possible to detect, by laboratory procedures, the presence of pyrogens in the finished preparations. In most of the others, the ingredients present interfere with the performance of the biological test; yet it is possible that pyrogens are present. Pyrogens are not necessarily affected by autoclaving. Bacteria-excluding filters may not remove pyrogens. It is for these reasons that pyrogen-free distilled water should be used in the preparation of all parenteral solutions. For record purposes, as well as for the assurance that pyrogens are absent, it is therefore necessary to check the distilled water used at frequent intervals. The distilled water is collected in a sterile container and sterilized in the autoclave at 121.3°C. for 20 to 30 minutes. The pyrogen test as given in the U. S. P. or N. F. is then performed.

(d) Other suitable vehicles than aqueous may be used. Fatty oils of vegetable origin, free of rancidity also are employed. They

should meet the U. S. P. and N. F. requirements for free fatty acids. All vehicles should be non-toxic and should not interfere in any way with the therapeutic efficiency of the active ingredients or with the assays and tests employed for the latter.

Added Substances

Various substances may be added to parenteral solutions to assure the usefulness or to prolong the shelf life of the preparation. Buffers may be incorporated to maintain the pH within a given range. They are frequently important to insure that the potency of the active ingredients is not altered or to avoid discoloration and the production of sediments. It is good practice to determine the most satisfactory pH range for each preparation. Injections of solutions of too low or too high pH values may produce discomfort or other undesirable reactions. Certain substances, such as concentrated sodium citrate solutions, unless buffered may extract silica from the glass containers which will cause deposition of insoluble material in the preparation. It may be that a stabilizer such as the use of calcium D-saccharate in Calcium Gluconate Injection is required. Sodium thiosulfate or a hypophosphite can be added to prevent or retard the discoloration of sodium iodide solutions. Urea or tryptophane may be used to increase the solubility of riboflavin.

A bacteriostatic agent must be added to all parenteral solutions in multiple dose containers and may be added to single dose containers filled aseptically. The antibacterial agent may be phenol, tricresol, chlorobutanol, an organic mercurial, etc. In all instances the substance should not only be present in a concentration to assure the prevention of growth of bacteria, molds, yeast and other organisms but also be harmless in the amount used.

All added substances must be non-toxic in the concentrations used, and they should not affect the therapeutic efficiency or interfere with the assay or response to other tests for the active ingredients.

Containers for Solutions

Great care must be taken in the selection of glass containers for parenteral solutions. They must be free of foreign particles, and the glass must be insoluble when in contact with the materials used during the processing and during its shelf life. In like manner they should be free of particles of glass which may not have been completely fused to the walls in the manufacture of the containers. Such

particles may be freed during heat sterilization procedures or after a prolonged contact with the solution. They must withstand the sterilization temperature employed without malformation of the container, and they must not in anyway alter the composition of the solution. For instance, a change in pH due to the container may affect the stability of a preparation or produce precipitation of the ingredients and occasionally discoloration. Careless handling and careless exposure of empty containers, especially to conditions which are far from sanitary, are to be avoided to be assured of the absence of broken glass, dust, dirt and foreign particles within the container. Manufacturers should check the glass used (even if only spot-checked) by performing the tests for Glass Containers, Types I, II, III, and IV as found in the U. S. P. and N. F. Other tests available or may be devised to note the presence or absence of glass and other particles after heat sterilization or after other treatment. The U. S. P. and N. F. list the suggested type of glass containers for many parenteral solutions.

Glass containers for parenteral solutions should be clear and colorless. If the contents are light-sensitive, each ampul or container can be placed in a carton impervious to light or may be constructed of light amber glass which permits an inspection of the contents.

Inasmuch as it is important that the sterility of the contents is not impaired, containers must be sealed or otherwise protected to exclude the possibility of contamination. Rubber caps or stoppers or other suitable closures are used especially for multiple dose containers. Frequently one finds that there is no choice but to use the stoppers made available by one or two manufacturers. The container and closure must not affect the contents in any manner under the conditions of handling and use. Closures for multiple dose vials should permit penetration by a needle. Upon withdrawal of the needle the closures must again close the container to prevent loss of contents or entrance of contaminants. Furthermore, penetration should be possible without detachment of fragments from the closure. To be always assured of the latter, nylon-covered rubber stoppers, and even better rubber stoppers coated on the inside with a plastic coating, have been suggested.

Preparation of Equipment

Painstaking care and attention must be given to the cleansing (and sterilization if necessary) of containers and equipment to be used for parenteral solutions.

(a) Glassware and in particular ampuls or vials must be washed carefully to be sure that all particles have been removed from the inside. The technique of washing may have to be selective for the different kinds of glass or for different types of containers. Boiling in a suitable (preferably neutral) detergent for an hour or longer is usually adequate. In other instances boiling in dilute alkali followed by dilute acid solutions yields better results. In all cases, such boiling treatment is followed by many rinses with distilled water, and the final rinsings are with injection water. Occasionally one finds glass containers which reveal a clouded appearance. This is usually due to minute amounts of grease or oil either in the air used to blow out ampuls or other containers, or it may be in the distilled water. It is important to see that only filtered air is used, that water pipe lines are cleaned before installation and that grease is not used on elbows, valves and fittings. Washed containers are placed neck downward in covered, dust-proof metal (preferably stainless steel) containers or in stainless steel wire baskets. The latter are wrapped. Small units are to be preferred to one or a few large containers. Wherever possible the empty containers are sterilized, immediately after washing, in a hot-air oven at 170°C. for 2 to 4 hours. Containers in metal boxes (free of inflammable material) can be heated at 200°C. to 250°C. for 1 hour. This sterilization procedure must be practiced in all instances if the containers are to be used in aseptic filling or in instances where they are not used immediately for filling of solutions followed by a sterilization technique. Such a procedure also will give greater assurance of the absence of pyrogens in individual vials, ampuls or other containers.

(b) Rubber stoppers for multiple dose vials are washed by a procedure similar to that used for empty containers, always followed by several rinsings of pyrogen-free water. A bendix or other suitable washer may be used. The last rinsings upon examination should reveal the absence of particles. In many instances, directions for cleaning stoppers are supplied by the manufacturer, who usually has available the most suitable procedures. The washed stoppers are placed in a covered wide-mouth bottle or in individual holes in a perforated tray which fits into a metal box, and they are sterilized in the autoclave at 121.3°C. for at least one-half hour.

(c) Aseptic filling requires the use of suitable filters or pads (pad filtration) which will remove bacteria by filtration of the

parenteral solution. They may be the candle type as the Berkefeld or Mandler filter, made of infusorial earth, or the Chamberland and Selas filters, made of specially treated porcelain. Pad filtration, as in the use of the Seitz or Hormann filter or press filtration arranged with a set of prefiltration pads, also is in common use.

Care is to be taken in the purchase and especially in the testing of the filters used. The manufacturer of this type of equipment usually supplies valuable information for the best procedure to handle and use it. It is not possible to give the details here. The important points to remember are to limit the volume of liquid passing through a filter and to avoid a high pressure. Filters should be thoroughly cleansed after each operation and before sterilization and fired frequently (after a few filtrations). New filters should always be tested to be sure they are not faulty. It is important to note in each instance that the filtration procedure does not alter in any way the solution passed through it. A change of pH, the adsorption of an active ingredient or the interaction of calcium or other substances from the filter or pads with the product may occur. Assays should always be made on the filtered product, not only on the preparation before filtration. Especially in the case of new filters or a new batch of pads, it is good practice to examine samples of the filtrate at a later date to note the absence of crystalline material or other suspended matter, and to be assured that alterations have not occured.

Sterilization Procedures

Adequate sterilization to be assured that the preparation and container are sterile and the contents are not altered in any manner is not always a simple problem. The techniques suitable for many of the commonly used medicaments are mentioned in most textbooks. Frequently however, where heat sterilization procedures are used, it may be necessary to conduct a series of tests to determine the most suitable methods for a given preparation. Physical examinations and assay or potency tests conducted before and after treatment usually supply the required information.

Those who operate sterilizers should be thoroughly familiar with their use and the principles involved in the sterilization techniques. The proper loading of sterilizers is of great import. The use of automatic recording devices is most helpful. The efficiency of the procedures should be checked constantly with the Diack control method and the potentiometer method of testing. Spot checks which

make use of cultures of resistant viable spore bearers should also be performed.

Other Quarters

The receiving room where raw materials and containers are received and unpacked, the washing room, the unit where visual inspection is done, the packing room and the quarters where laboratory testing is performed are each segregated from the compounding and filling rooms. However, the space should be so arranged to provide a continuity of movement of supplies that will avoid unnecessary work and confusion.

Controls

Control procedures which influence the quality of the finished preparation are carried out throughout all operations in a manner similar to that employed for all medicinal products. Additional specific control tests are necessary for parenteral solutions. Some of these were mentioned previously. Among the others, the following are important:

Volume in Containers

Ampuls and vials should be filled with an excess amount of the preparation to permit the withdrawal of the labeled volume as indicated. The new 1950 U. S. P. and N. F. include tables indicating the excess volumes to be used.

Number of Doses in Containers

There is a tendency to place a limitation on the size of containers for parenteral solutions. This is to reduce to a minimum the possibility of infections and untoward reactions. Single-dose containers are being suggested for all injections intended to be used for intracardial, intracisternal, intraspinal and intravenous administration. Multiple-dose containers may be used for solutions to be injected intracutaneously, intramuscularly or subcutaneously, but it is suggested that, wherever possible, the total volume be limited to the maximum of 10 usual doses of the preparation. Parenteral solutions official in the 1950 U. S. P. and N. F. will be governed by the above unless otherwise indicated in the individual monograph.

Clarity of and Undissolved Foreign Material in Solutions

Good manufacturing practice requires that parenteral solutions in each of their final containers should be individually inspected visually.

Even granting that the foreign particles are harmless, their presence reveals in many instances poor production procedures. One finds frequently a close relationship between insanitary conditions or inadequate control systems and the amount of undissolved foreign particles present. Purchasers of solutions containing foreign particulate matter frequently refuse to use these preparations.

Unfortunately an accurate mechanical method of detecting in clear solutions all foreign or particulate matter or so-called undissolved particles is not as yet available. Visual routine inspection as now practiced by plant personnel involves many problems. It is slow, tedious and the findings of different workers may vary. It also appears difficult to agree on what is to be regarded as a reject. Nevertheless until mechanized inspection is developed or an acceptable test method is forthcoming, it is incumbent upon manufacturers to set up a practical working procedure to be assured that their parenteral solutions are relatively free of foreign particles. Employees with good eyesight should be trained for this task. Eyes become fatigued during such inspections. Accordingly inspectors should be given 10 minute rest periods at the end of each hour, and no individual should do visual inspections for more than 2 hours in the morning and 2 hours in the afternoon in any 1 day. They may be assigned other duties for the remaining working period.

Clear, colorless solutions are to be free of turbidity, color, precipitates or sediment. Unfortunately these objectionable characteristics may appear only upon aging. This frequently may be due to the raw materials employed, when impurities or degradation products precipitate. It is therefore good practice periodically to examine control samples of packaged goods to observe whether abnormal changes have occured during their shelf-life.

Testing for Sterility

What constitutes acceptable and adequate evidence that the completed parenteral solution is sterile? In the final analysis, the manufacturer must assume the responsibility for this decision, as obviously it is not practical to examine each container.

In practice when testing for sterility, it is necessary to employ a minimum nummber of final containers from a single sterilizing or aseptic filling operation. Any number designated as the minimum for routine use can be only a suggestion, but it can be regarded as an effective indicator only after evaluation of other evidence. Any routine procedure should be supplemented periodically by more exhaustive tests, with larger volumes, more containers, an array of different media, other testing procedures and known positive controls. It is good practice occasionally to have outside laboratories check test the preparations. As important also is the necessity of placing greater emphasis on rigid plant inspections, competent personnel and the extreme care exercised in all plant operations and controls.

It is apparent from what has been said above that it is difficult to indicate the specific number to be tested unless all factors are considered including the economics. The routine testing of representative samples consisting of not less than 3 per cent of the total number but limited to the maximum of 10 containers from any one lot may be adequate if the other checks, mentioned above, were instituted. However, it is desirable to increase the number of representative samples to be tested if the other controls are inadequate. An increased number may also be advantageous for samples filled aseptically and where the batch or lot contains many thousands of ampuls or large numbers of containers.

For routine purposes, the procedure for testing liquids as given in the U. S. P. and N. F. is employed. The question is frequently asked whether it is necessary also to test routinely for molds. Here too it is well to again repeat the statement that adequate testing is the responsibility of the manufacturer. However, in an attempt to answer this specific question, each manufacturer can readily determine for himself just which preparation should be tested for molds. An investigational study with positive controls will supply the required data. In most instances where heat sterilization procedures in the final containers are employed and the temperatures used were 100°C. or higher, or in preparations containing suitable bacteriostatic agents, molds are rarely apt to be present. It is important to test preparations for molds especially if they are nutritive agents and bacteriostatic agents are absent in the preparation and if low heat sterilization or aseptic fill operations are used in manufacture. The best example is dextrose solution. Even if the test is negative when the minimum number of samples is used for routine

testing, it is good practice wherever possible to quarantine all containers in the lot or batch and to keep the samples in a warm room for 6 to 8 weeks. The visual inspection of each individual sample is then performed. If mold spores were present originally in a few containers, visible growth is now apparent upon examination.

It is important to recognize that various parenteral solutions may be contaminated and yet reveal a negative finding when employing the usual methods of testing for sterility. The solution may be inherently bacteriostatic due to a low pH or to a high concentration of certain salts. If this prevails, larger volumes of media must be used to test for sterility. To determine whether a preparation under test may be bacteriostatic in the amounts cultured, negative tubes after incubation for the 7 day period are inoculated with broth cultures of different viable organisms and these are incubated. Failure of growth is evidence that the preparation in the amounts used is bacteriostatic and is responsible for the negative results.

Matters concerning competent personnel and the thoroughness and excellency of technique mentioned previously apply as well to those concerned with the performance of all control tests. These individuals should be well trained and familiar with all details of the testing procedures in use.

Note

Space is inadequate to indicate, let alone detail, the many problems encountered in the manufacture of parenteral solutions. This brief presentation has been limited to a number of important considerations and indicates that high quality in such preparations requires constant vigilance and careful attention to all details.

POSSIBILITIES OF IMPROVING NICARAGUAN IPECAC ROOT BY SELECTION

By E. C. Higbee* and J. W. Kelly**

IPECAC root is the most important botanical crude drug exported by Nicaragua. It is obtained from wild plants growing in the tropical rain forests of the Departments of Chontales and Zelaya. Principal collection areas in those departments are in the vicinity of Santo Tomas, Muelle de los Bueyes and along the San Juan River at the Costa Rican frontier. Wild stands of ipecac are being gradually depleted in Nicaragua, it is claimed, owing to intensive exploitation. Consequently, the Nicaraguan Ministry of Agriculture has become interested in finding an economical and practical means of supplementing the wild stands with cultivated ipecac and requested the senior writer to undertake some studies in collaboration on such a project. This brief paper reports on an examination of the plants obtained from one locality for propagating purposes as a first step in such an undertaking.

Reports of experimental and commerical plantings of ipecac, *Cephaelis ipecacuanha* are summarized by Bal (1). Commercial cultivation of ipecac was first attempted in India after a living plant had been introduced to that country from Brazil via the Kew Gardens in 1866 (2). The Government Cinchona Plantation, Bengal, India, reported a harvest of 378 pounds of dry ipecac root for the year 1936-1937 (3). From India, ipecac was introduced to Johore and Selangor, Federated Malay States where experimental cultivation is said to have been successful although commercial production has not been large. In a report by the chief research officer of the Federated Malay States Department of Agriculture quoted by Bal (1), it is stated that long root cuttings were used as propagating material. These cuttings were rooted in shaded flats of specially prepared soil consisting of two-thirds sand and one-third humus. After two months they were pricked out about four inches apart in shaded flats filled with equal parts of sand and jungle mold. After six months the rooted cuttings were transplanted to shaded raised beds in which the soil was loosened to a depth of two feet. These transplants were

* Associate Professor, Department of Geography, Yale University.
** Biochemist, Division of Tobacco, Medicinal and Special Crops, P. I. S. A. E., U. S. Department of Agriculture.

spaced 12 to 16 inches apart. Surface soil about the plants was forked over to a depth of 2 to 3 inches at monthly intervals until harvest took place about 2½ years after transplanting to the permanent beds. Bal reports the analysis of air dry roots of 2½-year old plants grown by the Central Experiment Station, Serdang in Selangor State as follows: Moisture 9%, total alkaloids 3.1%, and emetine 1.6%.

The experience of growers in India and Malaya has shown it is both expensive and difficult to grow ipecac under artificial shade and in raised beds which require considerable preparation and constant weeding. These methods cannot be recommended to the Nicaraguan planter since they would be more costly than gathering wild roots. It is thought that a method of growing ipecac under forest cover should be devised. Such a method would obviate a cash outlay to clear land and provide artificial shade. It is expected that leaf litter and natural shade of the native forest will suppress most weeds, keep maintenance costs at a minimum as well as provide the normal environment for the plant's growth. To make even forest culture of ipecac as profitable as gathering wild plants, propagating stock of superior quality will be necessary.

In the latter part of April 1944, the area southeast of Muelle de los Bueyes on the Mico River was visited for the purpose of collecting living plants. These were found in a virgin forest area at an elevation of about 300 feet. The topography is gently rolling and well drained. A mulch of newly fallen leaves covered the surface of the ground but little humus appeared to be incorporated in the clay top soil which is of a cocoa-brown color and of a friable nut structure.

Rapid tests of soil samples taken from six locations in the area indicated that the available P_2O_5 is low throughout; the available K_2O is medium to high (4) and the pH 5.5 to 6.0 (5).

Herbarium specimens prepared from several of the plants collected in the area in April when the plants possessed neither flowers nor fruits have been tentatively identified as *Cephaelis ipecacuanha* (Brot.) A. Rich. by comparison with named specimens in the Smithsonian and National Arboretum herbaria.

While the area in which the plants were found was of limited extent, probably not more than one-quarter of a square mile, *C. ipecacuanha* was one of the common forest floor species. Inasmuch as the forest districts where ipecac is found in Nicaragua are combed by native root diggers more or less thoroughly each year the plants

gathered are not believed to have been more than one or two years old. They averaged about 10 to 12 inches in height. Occasionally stoloniferous stems spread over the ground under the leaf mulch for a foot or more and took root at irregular intervals. Only the principal roots were of commercial size. Those growing from the stolons had not had time to develop the thick annulated cortex which distinguishes mature roots.

Two hundred and sixty-eight plants were dug from spots selected at random during a 2-day period. These plants were removed from the soil with as much root as possible. The method of removing the plants from the ground was the same as that used by the native Nicaraguan diggers who collect the wild root for commerce. By this system the plant is grasped in one hand and pulled with slight tension while the roots are pried out by shoving a short sharp-pointed stick into the ground. The stick is worked back and forth to loosen the earth; then the plant is lifted by using the stick as a lever to push up the ground and the roots together.

The 268 individual plants were packed in moist sphagnum moss and transported to the United States-Nicaraguan Estacion Experimental Agricola at Recreo on the Mico River. There a planting site had been selected in a deeply shaded woods of virgin and second growth trees. None of the tree growth was disturbed but a few scattered ground covering plants were cut down. After trimming the tops back the ipecac plants were transplanted directly into holes in which the earth had been loosened to a depth of one foot. Only 39 plants had sufficient mature roots to provide material for at least a qualitative test for alkaloids. Each of these was trimmed of all but one-half inch of their root. The root clippings from each plant were tagged with the number of the plant from which they were taken.

After transplanting all the plants were watered two to three times a week for nearly one month until the annual rainy season began the latter part of May. Then they were permitted to shift for themselves. In planting, the leaf litter on the forest floor was disturbed as little as possible. Within 10 days after transplanting, owing to the constant fall of leaves, the ground was as evenly covered with litter as it was before being disturbed. The shade provided by the forest compared favorably with that from which the plants were taken and it was not expected that any hacking back of volunteer competitive growth would be necessary more than once a year.

In November, about six months after planting, 18 of the 268 planted were dead. An additional 4 plants were without leaves, although the stems were alive. The 39 from which roots were obtained for examination were all alive. The plants had had no care since they were transplanted with the exception of the waterings they received during the month of dry weather immediately after the transplanting.

The dried roots from each of the 39 individual plants selected for testing ranged in weight from 0.5 to 0.7 gms. These quantities were inadequate for individual assay but it was possible to obtain an approximate relative evaluation of the samples. The roots from each plant were powdered in a mortar and 0.3 gms. completely extracted with ammoniacal ether, filtered, washed with ether and the filtrate and washings evaporated to dryness on a steam bath. The residue was dissolved completely in 3 ml. of N/1 sulphuric acid. One ml. of the solution was transferred to a vial and 0.5. of Mayers reagent for alkaloids added. After the precipitate settled the clear liquid was tested for complete precipitation of the alkaloids. The precipitate was in each case collected on a Gooch crucible, washed, dried and weighed.

The weights of the precipitates do not show the actual amount of alkaloids present but they serve as a measure of the relative alkaloid content of the roots of the individual plants. The weights ranged from 5.2 to 31.2 mg. Fifteen samples gave from 5.2 to 9.9 mg., 20 from 10.4 to 17.6 mg and 4 from 21.6 to 31.2 mg. There is a clear indication therefore of a wide range of variation in the quality of the individual plants. The 39 samples were divided into two lots with lot 1 including the 19 which gave the most precipitate with the alkaloid reagent and lot 2 the remaining 20 which gave the least. All the ground root available from the samples in each lot was mixed thoroughly and assayed by the method recommended for ipecac alkaloids in U.S.P. XIII. The total alkaloid content found was 4.13 and 3.22 percent respectively. Inasmuch as these results are higher than the alkaloid content of ipecac root recorded in the literature, the titration solutions from the two lots were combined, made alkaline with strong ammonia and the alkaloids again extracted with successive portions of ether. The ether was evaporated and the alkaloidal residue dried and weighed. The 1.62 gms. thus obtained is equivalent to 3.1 percent.

It appears, therefore, that the quality of the roots of the plants selected for the propagation and improvement studies was good and that the isolation of superior clones of ipecac seems technically feasible.

REFERENCES

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SELECTED ABSTRACTS

Cepharanthine in the Treatment of Tuberculosis. Editorial. *Brit. Med J.* No. 4648:294 (1950). Studies in Japan have shown that the alkaloid cepharanthine ($C_{37}H_{38}O_6N_2$) has curative action on tuberculous infections in experimental animals and in man. The alkaloid is a light yellow powder with a melting point of 103°C and is found in the roots of *Stephania cepharantha* and in the stems of *S. sasakii,* both members of the Menispermaceae family. It may be administered orally or intravenously.

In a series of 290 cases of pulmonary tuberculosis in man there were 48.8 per cent of cures obtained. In lupus the effect was marked when 1 mg. was given daily. In laryngeal tuberculosis, and tuberculosis of the bone and genitourinary tract the results were not as obvious. However, in 10 of 11 cases of lesions of the eye the curative effects were classed as remarkable.

The alkaloid was also found to be effective as a prophylactic. In one plant a prophylactic treatment consisting of 0.1 mg. daily for one week, a rest period of one week and then a second course of treatment was given to 2,869 persons. During the next 8 months the incidence of new cases of tuberculosis was 0.14 per cent as compared with 37,040 untreated persons in the same plant who had a new case incidence of 3.48 per cent during the same period. Similar results were obtained among school children.

It was also stated the cepharanthine was effective in the treatment of leprosy when given by mouth. A group of 16 of 22 cases of macular and 13 of 27 cases of nerve leprosy were said to have been cured.

Proguanil Resistant Falciparum Malaria in Malaya. J. F. B. Edeson and J. W. Field. *Brit. Med. J.* No. 4646:147 (1950). Early trials of proguanil (Paludrine) in the treatment of falciparum malaria were very effective. Persons bitten many times by infected

mosquitos were protected by 100 mg. given every day. Heavy infections were cured by a 10-day course of 300 mg. a day. The drug was found to be effective against the pre-erythrocytic forms and against the asexual blood forms. Gametocytes exposed to therapeutic doses were so affected that sporogony in the mosquito was arrested. However, as use of the drug became more world-wide it became evident that there was variation in the sensitivity of different strains of falciparum malaria to proguanil. Also, evidence began to be observed that sensitivity of the parasites of a given strain began to wane with prolonged exposure.

In the Tampin district of Malaya proguanil was used sporadically but widely for two years previous to the observations of the authors. In 1947 they had observed no failures with single therapeutic doses of 100 to 300 mg. of proguanil but two years later there was one failure out of every 4 treated with a standard therapeutic course of 300 mg. a day for 5 days.

The authors stated that the development of resistance to this therapeutic agent appears to be in the asexual blood forms, transmissible through the gametocyte and sporozoite. The resistance seems most likely to arise when the drug is used to treat acute infections with subcurative doses or during haphazard suppression. It has been suggested that proguanil suppression be alternated with suppressive measures using mepacrine or chloroquine, which are not known to produce resistant strains. The authors suggested that unless the problems related to the use of proguanil in the treatment of falciparum malaria are solved the important role which this therapeutic agent has won may be lost.

Synergistic Effects of Sodium Iodide and Penicillin Against Spirochetes. J. A. Kolmer and A. M. Rule. *Arch. Dermatol. Syphilol. 61*:49 (1950). The authors first attempted to determine the minimum curative dose of penicillin and sodium iodide on experimentally induced syphilis in rabbits. They found that 8000 units of penicillin per Kg. of body weight given intramuscularly over an eight-day period were completely curative. When sodium iodide was given intravenously in divided doses to a total of 0.4 to 1.6 Gm. per Kg., or orally to a total of 0.8 to 2.4 Gm. per Kg., over the eight-day period, they found it to be only slightly spirocheticidal.

Combined therapy was then given to a third group of rabbits with experimentally induced syphilis. The dosage employed was 250 units of penicillin per Kg. intramuscularly twice a day for 8 days and 0.1 Gm. of sodium iodide per Kg. intravenously or orally twice a day for 8 days. This therapy was completely curative. Thus 4000 units of penicillin, half the minimum curative dose of penicillin alone, combined with a total of 1.6 Gm. of sodium iodide proved to be effective. From this evidence it would appear that penicillin and iodides act synergistically or additively in the treatment of experimental syphilis.

The authors stated that they felt that this combined therapy would be most valuable in the treatment of late acquired and congenital syphilis in human beings but that it would not be of particular value in the treatment of primary syphilis.

The Role of Aureomycin in Atypical Pneumonia. H. S. Collins, E. B. Wells, T. M. Gocke, and M. Finland. *Am. J. Med. 8:* 4 (1950). The effectiveness of aureomycin therapy in the treatment of "viral" or primary atypical pneumonia was investigated by the authors on a group of 49 consecutive cases. The patients were placed in groups based upon symptomatic diagnosis and the demonstration of cold agglutinins by serological methods. Group I included those patients having both symptomatic and serological identification of the disease; group II included those having clinical identification but not serological identification; and group III included those having serological but not symptomatic identification of atypical pneumonia. Group III patients were really not diagnosed, therefore, as having atypical pneumonia at the time of treatment.

Aureomycin was given orally. The optimum dose was not established but most of the patients received 1 Gm. every 4 or 6 hours. A total dosage of 10 to 15 Gm. given over a period of 3 to 4 days appeared to be adequate in all of the cases benefited. A number of the patients received the antibiotic on a schedule of 0.5 Gm. every 3 or 4 hours. The only side effects observed were gastrointestinal symptoms. However, in 13 of the patients there were no gastrointestinal disturbances from full doses. There was no clinical or laboratory evidence of any toxic effects on the blood, kidneys, liver or nervous system of any of the patients.

In groups I and II there was a definite and marked drop in temperature and an improvement in clinical symptoms in direct response to the administration of the aureomycin. The majority of the patients were afebrile by the second day of therapy. In 24 of the 40 patients in groups I and II the lungs were completely cleared within 10 days. The results in group III were less dramatic but among those in whom it appeared there had been atypical pneumonia later complicated by pneumococcal or mixed infections there was a definite but variable beneficial effect.

The authors concluded that aureomycin is a highly effective therapeutic agent in the treatment of primary atypical pneumonia.

Tonicity Values for Penicillin and Streptomycin Solutions. I. Michaels. *Pharm. J. 164*:95 (1950). The freezing point depression of solutions of penicillin and streptomycin were made using the Beckmann apparatus. The author found that for commercial batches of sodium penicillin there was a potency variation between about 1100 and 1400 units per mg. Therefore, the same solution concentration in units per cc. would have a different FPD depending upon the potency of the salt from which it was made. Consequently, the author experimentally prepared a normogram showing the relation between the concentration of the solution, the potency of the salt and the FPD of sodium penicillin solutions. A few of the factors taken from this graph are as follows: 10,000 units per cc. made from 1400 units per mg. salt has a FPD of 0.09°C; 10,000 units per cc. made from 1200 units per mg. salt has a FPD of 0.12°C.; 20,000 units per cc. made from 1400 units per mg. salt has a FPD of 0.18°C.; 20,000 units per cc. made from 1200 units per mg. salt has a FPD of 0.22°C.; 50,000 units per cc. made from 1400 units per mg. salt has a FPD of 0.45°C.; 50,000 units per cc. made from 1200 units per mg. salt has a FPD of 0.56°C.; 100,000 units per cc. solutions are all hypertonic for the potency of the salt given on the graph, which was between 700 and 1700 units per mg. salt.

No graph was developed for other penicillins nor for streptomycin but the author stated certain results. A solution containing 77,000 units per cc. of crystalline sodium penicillin G and another containing 98,000 units per cc. of benzyl penicillin each had a FPD of 0.56°C. A 2 per cent solution of streptomycin hydrochloride had a FPD of 0.56°C. while a 1 per cent solution had a FPD of 0.30°C. A 3.25 per cent solution of the calcium chloride complex of strep-

tomycin had a FPD of 0.56°C. while a 1 per cent solution had a FPD of 0.20°C. An 8 per cent solution of streptomycin sulfate had a FPD of 0.56°C. while a 1 per cent solution had a FPD of 0.08°C.

The Use of Dihydro-Beta-Erythroidine in Parkinsonism. S. Shapiro and A. B. Baker. *Am. J. Med.* 8:153 (1950). Parkinsonism (paralysis agitans) is a disease which manifests itself by muscular rigidity associated with a tremor. If not handled properly it will quickly lead to complete invalidism in many patients. The primary objective of medication has been the alleviation of rigidity. Atropine and related alkaloids have been the principal therapeutic agents employed.

Recently a new compound, dihydro-beta-erythroidine, has been used in combination with atropine to produce an augmentation of its effects. This new compound has a curare-like action on the neuromuscular junction and is the hydrogenated product of the alkaloid erythroidine, which is obtained from *Erythrina* L., a genus of trees and shrubs widely distributed over the tropics and subtropics of the entire globe.

After clinical evaluation on a series of patients who had been under observation and treatment for considerable time previously, certain facts were observed. The use of the new drug alone had little or no effect upon the symptomatology but when used as an adjunct to atropine therapy there was striking improvement in most cases. Discontinuance of the drug resulted in a recrudescence of symptoms and readministration again resulted in clinical improvement. The effect of the drug was almost entirely upon the rigidity with very little effect on the tremor and the oculogyric crises.

The procedure offering the best therapeutic results was found to be the administration of atropine with gradually increasing dosage until the maximum benefit was obtained. When a base line of improvement had been reached and maintained dihydro-beta-erythroidine was added. This drug was given in oral doses of 50 mg. four times a day. Improvement beyond the base line was usually observed within a week or two with a maximum benefit being reached within a month.

The toxic symptoms from this new drug consisted primarily of gastro-intestinal disturbances, visual disturbances, and dizziness. In only one patient were these symptoms severe enough to require discontinuance of therapy.

Streptomycin in Pulmonary Tuberculosis. N. C. Furtos. *U. S. Armed Forces Med. J. 1*:137 (1950). In a study of the effect of streptomycin on various types of pulmonary lesions the author reported that 7 critically ill patients were selected for treatment with streptomycin because of recent posthemoptoic spreads of progressive tuberculosis. Hemoptysis is commonly followed by a bronchogenic dissemination of blood containing tubercle bacilli into a new portion of the lung. A persistence or steady increase in the new area of infiltration with fever and weight loss indicates a progression of the tuberculous seeding.

The dosages of streptomycin employed was 2 Gm., 1 Gm. or 0.5 Gm. a day in single or divided intramuscular injections. The experience gained in this series and in others reported in the literature indicate that the 2 Gm. dose is too toxic and that it has no therapeutic advantage over the 1 Gm. or 0.5 Gm. doses. It was also shown in this series that regardless of whether the streptomycin was administered 5 times a day, twice a day, or once a day no apparent effect on the results was produced.

The problem of resistance is very evident in the treatment of tuberculosis with streptomycin. Patients develop resistance at varying rates. A recent survey of patients treated for 120 days with 2, 1, or 0.5 Gm. of streptomycin a day revealed that 70 per cent were resistant by the end of the treatment period, regardless of the size of dose. A relatively small percentage of the patients showed evidence of the development or resistance within 42 days. Consequently, 2 of the patients in this series were treated for but 42 days. Both patients showed no signs of the development of resistance. Both showed initial improvement and one continued to improve markedly but the other suffered a relapse. A second 42-day course of treatment in the latter patient brought no improvement but there was still no signs of resistance.

In this series 4 patients showed dramatic improvement, 1 moderate improvement, and 2 were complete failures. The author suggested that a 42-day course of 1 Gm. of streptomycin a day be used since therapeutic effectiveness seemed to be as great as with longer courses and there is less danger of the development of resistance. Also, in cases of relapse, a second course of treatment is more likely to be effective. The author, however, emphasized that this does not mean that all cases of posthemoptoic spreads should receive streptomycin. In some cases bed rest alone will bring resolution and in

other cases administration of penicillin for 7 to 10 days during the early stages of the posthemoptoic spreading may aid in the resolution. Only then, with the exception of massive spreads where time is a vital factor, should the administration of streptomycin be considered.

Therapy of Dermatologic Conditions With Coal Tar. F. P. Lowenfish. *N. Y. St. J. Med.* *50*:922 (1950). Coal tar has long been used in the treatment of various dermatologic conditions, but because of the messy and pungent nature of the material the degree of patient acceptance has been low. In addition, considerable irritation and sensitization has resulted from its use. Recent refinements in the preparation of coal tar has reduced these objectionable characteristics.

The author used a specially refined coal tar product in a 5 per cent concentration in a vanishing cream base in the treatment of a total of 51 cases of various dermatologic conditions. Of this group 11 were suffering from psoriasis, 5 from neurodermatitis, 8 from atopic eczema, 6 from seborrheic dermatitis, 11 from chronic recurrent contact dermatitis, 3 from allergic dermatitis, 4 from varicose eczema, and 3 from lichen planus. The plan of treatment involved weekly roentgen ray treatments of 50 r following the application of the coal tar cream. The patients with psoriasis did not receive the roentgen ray therapy. During the rest of the week the patients were instructed to apply the cream morning and evening.

The results of this treatment were rather striking. Of the 51 cases 41 showed marked or moderate improvement. The remaining 10 were only slightly improved or showed no improvement. Of the 10 showing no improvement 5 were patients with psoriasis. Two others in the unimproved group were patients with varicose dermatitis who healed but then suffered a relapse following which this treatment was of no value.

Effect of Hexamethonium Iodide on Gastric Secretion and Motility. A. W. Kay and A. N. Smith. *Brit. Med. J.* No. 4651: 460 (1950). A new compound, hexamethonium iodide (C6), appears to show promise as a therapeutic agent in the treatment of pep-

tic ulcer. The compound is the hexa derivative of the polymethylene-bistrimethyl-ammonium series of compounds.

Ten patients ranging in age from 22 to 52 years were used in this study to show the clinical effects of this compound. A dose of 100 mg. of C6 was given intramuscularly. This single dose produced an immediate fall in the secretion of hydrochloric acid with subsequent achlorhydria which lasted for as long as 3 hours. Doses administered at 3 4-hour intervals during the night reduced the night secretion by more than half and none of the patients complained of gastric ulcer distress during the night. The administration of C6 along with insulin prevented the increase of hydrochloric acid secretion which normally occurs following the injection of insulin. However, C6 did not prevent the histamine-induced secretion of hydrochloric acid. In a test of the effect on gastric motility C6 completely inhibited gastric contractions for periods of 3½ to 4½ hours. The longest spontaneous phase of quiescence normally expected would be 30 minutes. The authors stated that the cessation of gastric contraction and tonus waves is as complete as that resulting from vagal section.

Hexamethonium iodide is relatively free from side effects, having no curare-like action and little effect on the blood pressure, in the dosage employed.

The authors stated that hexamethonium iodide is more uniform in effect, more potent, and of longer duration than other drugs with a similar pharmacological action. They thus suggest that this drug may have valuable use in the treatment of peptic ulcer.

The Effects of Dimercaprol and Parathyroid Extract on the Subacute Distribution of Lead in Rabbits. K. R. Adam, M. Ginsburg, and M. Weatherall. *Brit. J. Pharmacol. Chemotherapy* *4*:351 (1949). It has previously been shown that dimercaprol (BAL) increases the excretion and alters the distribution of lead in rabbits when the BAL is given within 24 hours following the intravenous administration of lead as lead acetate. The authors, in order to determine the effect of BAL on a later phase distribution of lead, studied the effects of BAL and of parathyroid extract on a single intravenous injection of lead acetate (2.07 mg. per Kg. Pb), labeled with Pb 210, the BAL being given 8 to 18 days following the injection of lead acetate. By this time most of the lead remain-

ing in the body was found in the bones. Parathyroid extract had previously been suggested as an agent capable of mobilizing lead from bones.

The BAL was given intramuscularly in a dose of 12.5 mg. per Kg. dissolved in aqueous propylene glycol twice a day for 4 days. A portion of the rabbits so treated were also given 8 units per Kg. of parathyroid extract per day intramuscularly for 3 days. The effect of this treatment was small, resulting in only a very small increase in the urinary excretion of lead. At the end of 21 days the rabbits were all sacrificed and the content of lead in the various tissues of the body was determined. About 25 per cent of the original dose of lead was found in the bones but the only other tissues containing more than 1 per cent were the liver and bone marrow. The persistence of lead in the bone marrow no doubt has a relationship to the mechanism by which lead produces anemia. The variation in the lead content of the bones of the rabbits varied considerably from animal to animal. In fact, the variation between animals was greater than and any changes attributable to treatment. Thus, treatment with dimercaprol and parathyroid extract appears to have no useful effect in rabbits subacutely poisoned with lead.

Experimental Tolerance to Intrathecal Injections of Crystalline Penicillin. T. H. B. Bedford. *Brit. J. Pharmacol. Chemotherapy 4*:329 (1949). The intracisternal injection of 1,000 I. U. of crystaline sodium penicillin in 1 cc. distilled water, into dogs with an average weight of 8.7 Kg., elicited no irritation response. The cerebrospinal pressure remained essentially unchanged after 6 hours and the number of polymorphonuclear leucocytes never exceeded 50 per cu. mm. The response following the injection of a like volume and concentration of penicillin in normal saline was somewhat different. No symptoms of irritation to the nervous system were evident but the cerebrospinal pressure was raised and the number of polymorphonuclear leucocytes averaged 6,500 per cu. mm. Part of this irritation response was no doubt due to the normal saline itself for a 1 cc. injection produced a similar increase in cerebrospinal pressure and an average of 2,574 polymorphonuclear leucocytes per cu. mm.

When the concentration of penicillin was increased to 10,000 I. U. all 4 of the dogs in which normal saline was the vehicle developed generalized convulsions within one hour. In a series of 12 dogs in which the vehicle was distilled water only one dog developed general convulsions but all of the others showed evidence of nervous system irritation. Thus it would appear that normal saline is not a good vehicle for the intracisternal injection of penicillin.

The irritant effect of penicillin on the nervous system seems to be of relatively short duration, for the animals appeared to be normal one hour after the injection. The irritant effect of sodium chloride solution seemed to be confined to the covering membranes of the nervous system and possibly to the arachnoid villi. However, penicillin rapidly penetrates the membranes with the production of relatively little irritation. Its main action is on the nerve cells.

Treatment of Functional Dysmenorrhea With Vasodilators. M. I. Griffith and J. M. Little. *South Med. J. 42:*1082 (1949). The cause of the pain of functional dysmenorrhea has been postulated by many theories. The inaccuracy of diagnosis has contributed to the confusion. The characteristic of vasodilation has appeared in many of these theories. The authors investigated the effect of vasodilators on the pain of dysmenorrhea and substantiated the part of vasodilation in the syndrome. Although the mechanism of relief of pain by the three vasodilators used in this study is not known, a possibility suggested is that the pain is produced by a stimulation of the nerve endings in small blood vessels as a result of vasospasm. A painful stimulus resulting from some other cause, such as uterine contraction, could cause a reflex vasospasm via the sympathetic nervous system.

The authors treated 22 patients with severe dysmenorrhea who had not responded to the usual methods of treatment. Vasodilators were given through 109 days of expected menstrual pain. Etamon (tetraethyl-ammonium) was given to 4 patients. Only one responded with complete relief of pain. Eighteen patients, representing 84 menstrual days, were treated with oral doses of Priscoline (2-benzyl-4,5-imidazoline hydrochloride). The dosage employed was 50 or 25 mg. The relief of pain was complete to partial in 95.4 per cent of

the menstrual days on which 25 mg. of the drug were given, a result slightly better than obtained with the 50 mg. dose. In addition, the 50 mg. dose produced rather severe vomiting in about half the patients. A total of 16 individuals representing 41 menstrual days were treated with intravenous Pricoline, intravenous nicotinic acid, or both. There was only 1 complete failure. The authors suggested that, particularly with oral therapy, those patients obtaining only partial relief could obtain better relief if a gastro-intestinal antispasmodic or an analgesic were combined with the therapy.

BOOK REVIEWS

A Concise Laboratory Manual and Atlas for Comparative Anatomy By W. H. Atwood. The C. V. Mosby Co., St. Louis, Mo. 1949. 114 pages plus 39 plates. Price $2.75.

This new laboratory manual in comparative anatomy is written primarily to accompany the author's *Concise Comparative Anatomy*. The material is arranged in the comparative order, i.e. each system is considered as a unit. For example, the chapters titled The Skull, The Vertebral Column, The Muscular System, etc., describe the structures and systems as they exist in Squalus, Necturus, Bullfrog and Cat. Another table of contents is provided for those who wish to follow the type method of dissection (i.e. for each animal type the pages are listed for the descriptions of the various systems).

The illustrations of the manual show a wide variety of style and artistic techniques. Some are complete, but some are left to be completed, colored and labeled by the student.

The manual should be appreciated by all comparative anatomy students for its clear concise descriptions and its illustrations which will give them more time for dissections and study. It also answers many questions usually asked of the laboratory instructor and will give him more time for all the students.

F. M. White

The Chemistry of Organic Medicinal Products, Third Edition. By Glenn L. Jenkins and Walter H. Hartung; 745 pages incl. index. John Wiley & Sons, Inc., New York; Chapman & Hall, Ltd., London $7.50.

This is the latest edition of a text which has been popular with both students and teachers of pharmaceutical chemistry since the introduction of the first edition in 1941. As in previous editions it is written with the assumption that those using the book have had a basic course in organic chemistry. The authors present in a clear and concise style the important medicinal organic compounds as well as closely related substances which have important physiologic

activity or are used as the starting point in important syntheses. The properties, uses and methods of manufacture are presented and a correlation made with the official title of the substance, provided it is recognized in the U. S. P. XIII or the N. F. VIII.

The text has been brought up to date and many new drugs, both natural and synthetic, are included.

With proper deletions of material the text might well be used for undergraduate students and it is particularly useful for advanced students in pharmaceutical chemistry.

A few typographical errors and omissions may be found but these are relatively few in comparison with the material which it contains. The text continues to be one of the outstanding works in its field.

L. F. Tice

Surface-active Quaternary Ammonium Compounds. By C. A. Lawrence, Ph. D., 245 pages, 9¼" x 6¼". New York, Academic Press Inc. Price: $6.00.

Probably no other person has made a more thorough presentation of quaternary ammonium surface-active antiseptics than has the author of this book. It is a most comprehensive presentation of the history, chemistry, physical properties, pharmacology and toxicology, biology and application of the quaternary ammonium salts in medicine, public health and industry.

The monograph is divided into eleven sections, followed by a thorough bibliography and author and subject indices.

The section on chemistry includes the synthesis, ionization, compatibilities, action on metals and chemical assay methods of the quaternary compounds. The Biological Section discusses bactericidal efficiency, infection-protection tests and sporicidal, fungicidal, virucidal and protozoacidal activities of these compounds.

The surgical uses of quaternaries are discussed pertaining to preoperative techniques, instrument sterilization, wound irrigation, urology, obstetrics and gynecology, ophthalmology, oralogy, and dermatology.

The Section of General Disinfection considers the use of quaternaries in eating and drinking establishments, the dairy industry, food processing plants, water purification and in oil emulsions.

Miscellaneous uses are referred to in the poultry and fish hatcheries; the textile, laundry, paper and mining industries; as well as in the preservation of plants and organic matter.

The book is recommended to all workers in scientific fields because of the fine presentation pertaining to the important place the quaternary ammonium surface active compounds have secured in medicine and industry during the past decade.

B. Witlin

Penicillin, Its Practical Application (2nd Edition). Edited by Alexander Fleming. xii + 491 pages. The C. V. Mosby Co., St. Louis, Mo., 1950. Price: $7.00.

The second edition of this work, which was first published in July 1946 under the editorial supervision of the discoverer of penicillin, is designed to record current thought regarding its applications. Material is divided into two sections, general and clinical, of which the clinical aspects occupy three times as many pages as the general. Only such information that will be of direct utility to the person who uses penicillin is included, but the history, chemistry, manufacture, pharmacy, pharmacology, bacteriological control and methods of administration are briefly summarized. Although the monograph is primarily concerned with penicillin, one chapter is devoted to streptomycin, and the appendix contains a short discussion of aureomycin and chloramphenicol.

The employment of penicillin in human medicine, dentistry and animal medicine is given very extensive treatment; those who use penicillin in these areas will find a wealth of information thoroughly supported by recent references at the end of each chapter.

N. Hall

The Chemistry of Industrial Toxicology. By Hervey B. Elkins. 406 pages. John Wiley & Sons, Inc., New York, 1950.

There are many texts written about poisons from a medical or medico-legal viewpoint. This book seeks to provide a practical chemical study of toxic substances as they are directly related to in-

dustry. There are essential differences in aspects to be emphasized in consideration of industrial poisons as opposed to medicinal, homicidal and suicidal agents. Routes by which the poisons usually enter the system are different, and remedial measures are directed primarily toward control of exposure.

A concise discussion of the fundamentals of industrial poisoning and problems in evaluation of toxic hazards introduce the material which follows. The second portion of the book deals with actually and potentially toxic chemicals industrially encountered. Poisons are treated as individual elements, compounds or groups, and a tabulation of harmful effects of the agent, degree of toxicity, maximum allowable concentration and methods of evaluation is given. Poisons are divided into three groups for presentation; inorganic chemicals, organic chemicals and natural industrial substances. Next, consideration is given to preventive measures, the concept of maximum allowable concentrations and certain fallacies, followed by air sampling devices including diagrams and photographs. A large section on analytical procedures described in a brief, easily followed manner concludes the volume. Each method contains one reference to one of the 366 papers in the bibliography.

As one reads the book he must be impressed by the efficient arrangement which increases its value to the industrial engineers and chemists for whom it is designed. It should find wide acceptance by those concerned with control of poisons produced and used by industry.

N. Hall


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